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Toll-like receptors 2 polymorphism is associated with psoriasis: A case-control study in the northern Chinese population

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Abstract

Background: Psoriasis is a disease caused by genetics and immune system dysfunction, affecting the skin and joints. Toll-like receptors (TLRs) play an important role in triggering the innate immune response and controlling adaptive immunity. The role of TLR2 in the progression of psoriasis is not well understood. **Methods:** A case-control study was conducted on a northern Chinese Han population, consisting of psoriasis patients and healthy control subjects. Genotyping was performed using the tetra-primer amplification refractory mutation system-polymerase chain reaction (ARMS-PCR), and allele and genotype frequencies of four SNPs in TLR2 were analyzed in 270 psoriasis patients and 246 healthy controls. **Results:** Four TLR2 SNPs (rs11938228, rs4696480, rs3804099, rs5743699) were genotyped and found to be in linkage disequilibrium. The genotype distributions of rs11938228 and rs4696480 in two groups were in Hardy-Weinberg equilibrium and statistically significant except for the overdominance model. The haplotypes ATTC and ATCC were found to be protective against psoriasis. **Conclusion:** Our study found a correlation between TLR2 genetic variations and the likelihood of psoriasis in northern China.

Keywords

Toll-like receptors 2; psoriasis; polymorphism; susceptibility

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1 Introduction

Psoriasis, a chronic inflammatory skin disease, is challenging to treat and often persists for a lifetime, imposing a significant burden on individuals and society[1]. It is estimated to affect approximately 1.7% of the global population, with higher incidence rates in the US and European populations (around 3%) compared to Chinese or asian populations (around 0.5%)[2]. Scientific studies have consistently shown that psoriasis development is closely associated with immune-mediated mechanisms. Specifically, the abnormal activation and migration of immune cells contribute to skin inflammation and the excessive growth of keratinocytes, leading to the formation of erythematous, scaly plaques of varying sizes[3]. Unfortunately, there is currently no known cure for psoriasis. The condition can be triggered by various factors, including skin damage, infection, stress, and certain medications such as beta-blockers, Non-steroidal anti-inflammatory drugs (NSAIDs, methotrexate, and imiquimod[4].

Toll-like receptors (TLRs) are a critical type of molecular pattern recognition receptors that are essential for initiating molecular cascades upon binding their ligands. This binding results in a conformational change and subsequent signal transmission to the nucleus, leading to the transcription of genes responsible for producing proinflammatory cytokines, adhesion molecules, and co-stimulatory molecules. These components are crucial components in the development of the adaptive immune response[5-7]. TLR2, a member of the TLR family, is expressed on the surface of various cells, such as macrophages, neutrophils, and lymphocytes[8]. The expression and activation of TLR2 in lymphocytes can significantly impact the function of T and B cells in autoimmune diseases. Studies have indicated an increased expression of TLR2 in peripheral blood monocytes and keratinocytes in psoriasis[9-10], suggesting a potential role in the disease. However, further research is required to elucidate the precise role of TLR2 in psoriasis.

Family studies strongly suggest that the development of psoriasis involves a genetic component. Recent genome-wide association (GWA) studies[11-13] and data from high-density SNP panels have identified 41 psoriasis-associated loci[14]. However, it is widely acknowledged that there are likely many more genetic loci yet to be explored. A study conducted in southern China revealed a correlation between the TLR2 SNP (rs3804099) and the heritability of plaque psoriasis[15]. Another study in Turkey found a strong association between the TLR2 SNP (rs4696480) and psoriasis genetics[16]. These findings suggest that the role of TLRs in disease incidence, pathogenesis, and clinical outcome can be influenced by population genetics. This study aimed to investigate the frequency of TLR2 SNPs in a population of psoriasis vulgaris (PsA) patients in northern China, as it has been observed that the environment, climatic conditions, and lifestyles of northerners and southerners differ, and the incidence of psoriasis in northern China is significantly higher.

2 Materials and Methods

2.1 Subjects

This study involved 270 patients diagnosed with PsA, consisting of 104 females and 166 males, with a mean age of 38.17 ± 9.90 years. Additionally, 247 healthy subjects were included, comprising of 105 females and 142 males, with a mean age of 37.94 ± 9.70 years. All specimens were obtained from the Second Affiliated Hospital of Harbin Medical University and confirmed through histopathological examination of paraffin-embedded tissue specimens. Blood samples from controls and tissue samples from patients were genotyped. The study ensured that all participants were matched in terms of age and sex. Clinical diagnoses were made by at least two dermatologists and confirmed by skin biopsy. Subjects' basic information, such as gender and age, as well as clinical data, including age at onset, Psoriasis Area and Severity Index (PASI) scores, and family history (including third-degree relatives), were collected through medical records and questionnaires. The questionnaire revealed that the subjects and their tertiary relatives were of Han ethnicity and hailed from the northern Chinese provinces of Heilongjiang and Jilin. None of the participants had any systemic, infectious, autoimmune, atopic, or malignant disease. The Ethics Committee of the Second Affiliated Hospital, Harbin Medical authorized the study protocol (GZR2023-06), and all study participants signed informed consent forms.

2.2 DNA isolation and SNP genotyping

Blood samples were preserved in tubes with ethylenediaminetetraacetic acid (EDTA) before genomic DNA extraction for genotyping. The QIAampDNA Blood Mini Kit from Qiagen was used for DNA extraction, and the samples were stored at -20°C. Four TLR2 SNPs (rs11938228, rs4696480, rs3804099, and rs5473699) were selected for genotyping. Genotyping was performed through multiplex PCR with sequence-specific primers, followed by purification of the amplified product using ExoI/SAP double enzyme digestion. The purified product was then used as a template for the ligation reaction. The primer sequences are provided in Table 1 and Table 2. Genotyping was conducted using the modified multiplex ligation-dependent amplification method (iMLDR) developed by Genesky.

2.3 Statistical analysis

Demographic characteristics, genotype, and allele frequencies of two groups were analyzed using SPSS 20.0 software (SPSS Inc., Chicago, IL, USA). The Pearson chi-square test was employed to evaluate codominant, dominant, recessive, and overdominant models and to determine Hardy-Weinberg equilibrium. Additionally, odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. Haplotype frequencies of TLR2 were determined using the expectation-maximization algorithm from SNPStats (http: //bioinfo.iconcologia.net/SNPstats). Pairwise linkage disequilibrium (LD) was evaluated using SHEsis (http: // shesisplus.bio-x.cn/SHEsis.html) by computing D' and quadratic correlation (R^2). D' was calculated as the ratio of the unnormalized D value to its maximum/minimum value. *P* values were adjusted using the Bonferroni correction test. Differences at $P < 0.05$ were considered statistically significant.

3 Results

3.1 The demographic characteristics of the population of interest

The study revealed that the selected polymorphic sites were in Hardy-Weinberg equilibrium. As shown in Table 3, the mean ages for the control and patient groups were 37.94 ± 9.70 and

Table 1 Sequence of primers

Primer position	Primer sequence (5'-3')
s11938228	
Forward primer	GGGGCAAGAATAACCAAGACACA
Reverse primer	GACATGCCCATATAGGGGTAGATCTTG
rs4696480	
Forward primer	GGTTCTGGAGTCTGGGAAGTCCA
Reverse primer	ACTGCGAGCTGAGAGGTGGAAC
rs3804099	
Forward primer	TGCAAATCCTGAGAGTGGGAAAT
Reverse primer	TCCAAACATTCCACGGAACTTG
rs5743699	
Forward primer	AGGATGCCTGGCCCTCTCTACA
Reverse primer	TGTCTTGGGAATGCAGCCTGTT

Table 2 iMLDR probe sequences

SNP allele	Primer sequence (5'-3')	LDR product
s11938228_modify	TCTATCCCTATACCAGCAACACACTATATTAAA TTTTTTTTTTT	63.21
s11938228_C	TTCCGCGTTCGGACTGATAT TCAGTGCTATTCTGATCCAATGTTCATGTG	67.77
s11938228_A	TACGGTTATTCGGGCTCCTGT TCAGTGCTATTCTGATCCAATGTTCATGTT	66.56
rs4696480_modify	GAGGGTCATCTGGCTACATTATAACATG TTTTTTTTTT	63.95
rs4696480_A	TCTCTCGGGTCAATTCGTCCTT CAAGATTGAAGGGCTGCATCTCGA	68.65
rs4696480_T	TGTTCGTGGGCCGGATTAGT CAAGATTGAAGGGCTGCATCTCGT	67.70
rs3804099_modify	GTAAGTCATCTGATCCTTCATATGAAGCA TTTTTTTTT	63.00
rs3804099_C	TTCCGCGTTCGGACTGATAT GAGCCAAAAAGTTTGAAGTCAATTCAGTAC	66.86
rs3804099_T	TACGGTTATTCGGGCTCCTGT GAGCCAAAAAGTTTGAAGTCAATTCAGCAT	66.40
rs5743699_modify	TGAGCAAAGTCTCTCCGGTTTTT TTTTTTTTT	63.53
rs5743699_C	TCTCTCGGGTCAATTCGTCCTT TCTTACTGATATCAATGTTAGTCAAGTTTTTCACAG	64.81
rs5743699_T	TGTTCGTGGGCCGGATTAGT TCTTACTGATATCAATGTTAGTCAAGTTTTTCACAA	65.02

Table 3 Demographic characteristics of the studied population

Characteristic	Cases, (*N* = 270)	Controls, (*N* = 247)	*P*
Gender, *N* (%)			
Male	166 (61.5)	142 (57.5)	0.3706
Female	104 (38.5)	105 (42.5)	
Age, years	38.17 ± 9.90	37.94 ± 9.70	0.7890
PASI, *N* (%)			
≤ 10	223 (82.6)	-	-
> 10	47 (17.4)	-	-
Age at onset, *N* (%)			
≤ 40 years	219 (81.1)	-	-
> 40 years	51 (18.9)	-	-
Family history, *N* (%)			
Yes	102 (37.8)	-	-
No	168 (62.2)	-	-

Data were presented as *N*(%).

38.17 ± 9.90 years, respectively. There were no significant differences in gender ratio and mean age between the two groups ($P > 0.05$). The majority of patients in the case group exhibited mild severity, with 82.6% of patients having a PASI score ≤ 10. Among all patients, 81.1% experienced onset before the age of 40. Moreover, 62.2% of patients did not report any family history of psoriasis.

3.2 Single SNP association analysis

The results of the study indicated that the rs11938228 mutation was linked to a higher risk of psoriasis under the dominant model (C/A-A/A *vs.* C/C; adjusted $P = 0.0041$), recessive model (A/A *vs.* C/C-C/A; adjusted $P = 0.0027$), and codominant model (adjusted $P = 0.0016$) (Table 4). Furthermore, variations in the frequency of the rs4696480 genotype were observed between psoriasis patients and controls in the dominant (A/T-T/T *vs.* A/A; adjusted $P = 0.017$), recessive (T/T *vs.* A/A-A/T; adjusted $P = 0.015$), and codominant models (adjusted $P = 0.012$). No significant differences in allele frequencies or genotypes of TLR2-rs5743699 and rs3804099 were identified between the psoriasis and control groups.

3.3 Distribution of haplotypes between cases and controls

Table 5 illustrates the frequency distribution of haplotypes, indicating that the ATTC and ATCC haplotypes were associated with an elevated risk of psoriasis across all haplotype models (rs11938228, rs4696480, rs3804099, rs5743699) (adjusted $P = 0.005$ and 0.04, respectively).

LD analyses were performed by calculating D' and R^2 values, with the results presented in Tables 6 ,7 and Fig. 1. In the psoriasis cases, all SNPs exhibited strong linkage, with D' values exceeding 0.8 and R^2 values exceeding 0.5.

4 Discussion

This study genotyped four TLR2 SNPs in 270 psoriasis patients and 247 healthy controls to examine associations between rs44696480, rs11938228, rs5743708, and rs3804099 with psoriasis. Significant allele frequency differences were found for rs4696480 and rs11938228. Different genetic models (dominant, recessive, co-dominant) all suggested associations with psoriasis, except for the overdominant model. Haplotype analysis further supported significant associations of these SNPs with psoriasis. Moreover, SNPs within patients exhibited strong LD. Overall, the findings prompted us to conclude that SNPs at the TLR2 locus were linked to psoriasis risk in Northern Chinese individuals, indicating a potential target for psoriasis therapy.

The TLR2 rs4696480 polymorphism, located at chr4: 153685974, has been linked to bacterial meningitis[17] and atopic dermatitis[18]. A study on Danish psoriasis patients undergoing biologic agent treatment for TLR2 and TLR9 variants revealed

Table 4 Allele and genotype frequencies of TLR2 SNPs in the case and control groups

SNP	Model		Controls	Cases	OR (95% CI)	*P*	*P**	OR (95% CI)	*P*#
rs11938228	Codominant	C/C	56 (22.7)	91 (33.7)	1.00	0.00180	0.0072	1.00	0.0016
		C/A	124 (50.2)	135 (50.0)	0.67 (0.44-1.01)			0.66 (0.43-1.00)	
		A/A	67 (27.1)	44 (16.3)	0.40 (0.24-0.67)			0.40 (0.24-0.66)	
		C	236 (47.8)	317 (58.7)	1.00	0.00054	0.0022		
		A	258 (52.2)	223 (41.3)	0.64 (0.50-0.82)				
	Dominant	C/C	56 (22.7)	91 (33.7)	1.00	0.00530	0.0212	1.00	0.0041
		C/A-A/A	191 (77.3)	179 (66.3)	0.58 (0.39-0.85)			0.57 (0.38-0.84)	
	Recessive	C/C-C/A	180 (72.9)	226 (83.7)	1.00	0.00270	0.0108	1.00	0.0027
		A/A	67 (27.1)	44 (16.3)	0.52 (0.34-0.80)			0.52 (0.34-0.80)	
	Overdominant	C/C-A/A	123 (49.8)	135 (50.0)	1.00	0.96000	1.00	1.00	0.9100
		C/A	124 (50.2)	135 (50.0)	0.99 (0.70-1.40)			0.98 (0.69-1.39)	
rs4696480	Codominant	A/A	57 (23.1)	87 (32.2)	1.00	0.01300	0.052	1.00	0.0120
		A/T	125 (50.6)	136 (50.4)	0.71 (0.47-1.08)			0.70 (0.46-1.06)	
		T/T	65 (26.3)	47 (17.4)	0.47 (0.29-0.78)			0.47 (0.28-0.78)	
		A	239 (48.4)	310 (57.4)	1.00	0.00400	0.016		
		T	255 (51.6)	230 (42.6)	0.70(0.54-0.89)				
	Dominant	A/A	57 (23.1)	87 (32.2)	1.00	0.02000	0.08	1.00	0.0170
		A/T-T/T	190 (76.9)	183 (67.8)	0.63 (0.43-0.93)			0.62 (0.42-0.92)	
	Recessive	A/A-A/T	182 (73.7)	223 (82.6)	1.00	0.01400	0.056	1.00	0.0150
		T/T	65 (26.3)	47 (17.4)	0.59 (0.39-0.90)			0.59 (0.39-0.91)	
	Overdominant	A/A-T/T	122 (49.4)	134 (49.6)	1.00	0.96000	1.00	1.00	0.9000
		A/T	125 (50.6)	136 (50.4)	0.99 (0.70-1.40)			0.98 (0.69-1.38)	
rs3804099	Codominant	T/T	123 (49.8)	121 (44.8)	1.00	0.52000	1.00	1.00	0.5300
		C/T	106 (42.9)	127 (47.0)	1.22 (0.85-1.75)			1.21 (0.85-1.74)	
		C/C	18 (7.3)	22 (8.2)	1.24 (0.63-2.43)			1.26 (0.64-2.46)	
		T	352 (71.3)	369 (68.3)	1.00	0.30700	1.00		
		C	142 (28.7)	171 (31.7)	1.15 (0.88-1.50)				
	Dominant	T/T	123 (49.8)	121 (44.8)	1.00	0.26000	1.00	1.00	0.2600
		C/T-C/C	124 (50.2)	149 (55.2)	1.22 (0.86-1.73)			1.22 (0.86-1.72)	
	Recessive	T/T-C/T	229 (92.7)	248 (91.8)	1.00	0.71000	1.00	1.00	0.6800
		C/C	18 (7.3)	22 (8.2)	1.13 (0.59-2.16)			1.15 (0.60-2.19)	
	Overdominant	T/T-C/C	141 (57.1)	143 (53.0)	1.00	0.35000	1.00	1.00	0.3600
rs5743699		C/T	106 (42.9)	127 (47.0)	1.18 (0.83-1.67)			1.18 (0.83-1.67)	
		C/C	245 (99.2)	268 (99.3)	1.00	0.93000	1.00	1.00	0.8600
		C/T	2 (0.8)	2 (0.7)	0.91 (0.13-6.54)			0.84 (0.12-6.05)	
		C	492 (99.6)	538 (99.6)	1.00	0.93000	1.00		
		T	2 (0.4)	2 (0.4)	0.91 (0.13-6.54)				

Data were presented as N(%). *P*: model-based statistical *P* value, *P**: *P* value adjusted Bonferroni correction, *P*#: *P* value adjusted by age and sex; OR: odds ratio; 95% CI: 95% confidence interval.

that TLR2 variants, rs11938228 and rs4696480, may play a role in psoriasis susceptibility[19]. Within the TIR domain of TLR2 lies a non-synonymous SNP, rs5743708, leading to an Arg753Gln missense mutation that impairs signaling[20]. This SNP, extensively researched, is associated with conditions like psoriasis and other skin disorders[16,21-24]. Additionally, the rs3804099 SNP, located in exon 3, causes a synonymous variation (Asn199Asn) and has been shown to reduce TNF-α, IL-1b, and IL-6 levels[25], suggesting a potential anti-inflammatory effect.

The present study examined the relationship between TLR2 rs11938228 and rs4696480 and psoriasis susceptibility in the North China population. Results indicated that individuals with the AA genotype of TLR2-rs4696480 may have a higher risk of psoriasis, while TLR2-rs11938228 polymorphism did not show a significant association with psoriasis risk[16]. In a separate study, a Chinese team investigated the impact of TLR2 and TLR4 polymorphisms on patients with PsA in southern China. The researchers found that only one of the six common SNPs they selected (rs3804099) was significantly linked to psoriasis risk[26], which is contrary to our findings. This discrepancy

Table 5 Haplotype association with psoriasis

	rs11938228	rs4696480	rs3804099	rs5743699	Total	Frequency in control	Frequency in cases	OR (95% CI)	*P*	*P**	OR (95% CI)	*P*#
1	A	T	T	C	0.44	0.48	0.40	0.713 (0.557-0.912)	0.007	0.113	0.705 (0.551-0.902)	0.005
2	C	A	C	C	0.28	0.25	0.30	1.262 (0.960-1.661)	0.095	1.000	1.236 (0.941-1.623)	0.126
3	C	A	T	C	0.24	0.21	0.26	1.299 (0.974-1.732)	0.075	1.000	1.328 (0.994-1.775)	0.054
4	A	T	C	C	0.01	0.02	0.01	0.248 (0.067-0.916)	0.024	0.383	0.225 (0.047-1.068)	0.04
5	C	T	T	C	0.01	0.01	0.01	2.512 (0.623-10.133)	0.180	1.000	2.461 (0.649-9.329)	0.171
6	A	A	T	C	0.01	0.01	0.01	1.289 (0.334-4.975)	0.711	1.000	1.144 (0.305-4.287)	0.84
7	C	T	C	C	0.01	0	0.01	1.836 (0.382-8.831)	0.441	1.000	1.835 (0.334-10.067)	0.477
9	A	T	T	T	0	0	0	0.027 (0.001-0.507)	0.267	1.000	-	-

*P**: *P* value after Bonferroni correction; *P*#: the OR and *P* values were adjusted for age and sex.

Table 6 Analysis of linkage disequilibrium based on evaluation of D' in patients

	rs11938228	rs4696480	rs3804099	rs5743699
rs11938228	-	0.948	0.869	0.961
rs4696480	-	-	0.852	0.956
rs3804099	-	-	-	0.449
rs5743699	-	-	-	-

Table 7 Analysis of linkage disequilibrium based on R^2 statistics in patients

	rs11938228	rs4696480	rs3804099	rs5743699
rs11938228	-	0.885	0.285	0.004
rs4696480	-	-	0.278	0.004
rs3804099	-	-	-	0
rs5743699	-	-	-	-

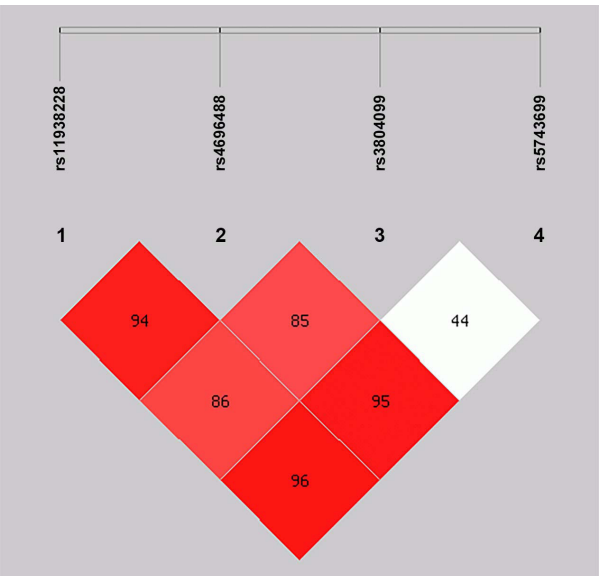

Fig. 1 Linkage disequilibrium analyses

may be due to differences in psoriasis inheritance patterns may differ across ethnic or regional groups, underscoring the importance of considering other factors in studying genetic associations with psoriasis risk.

Some genetic polymorphisms can render patients insensitive to conventional treatments like methotrexate, retinoic acid, cyclosporine, and physical therapy. However, this study did not observe any effect of TLR2 polymorphisms on patient treatment outcomes. It is important to note that the findings of this study were constrained by the sample size, indicating a need for further validation.

The analysis of four SNP loci revealed significant LD, suggesting a connection between TLR2 and psoriasis in terms of gene frequency and haplotypes. Certain haplotypes, like ATTC and ATCC, were identified as protective against psoriasis. This initial insight sheds light on TLR2's involvement in psoriasis development, but further research is needed to investigate the specific mechanisms. The functions of these haplotypes in psoriasis and other immune diseases are still unclear.

5 Conclusions

Our study revealed a significant association between the TLR2 gene's rs11938228 and rs4696480 polymorphisms and susceptibility to PsA in northern Chinese patients. The identification of these genetic markers may aid in the discovery of new diagnostic and therapeutic targets for psoriasis. Nonetheless, additional research is required to assess the expression levels of biomarkers in blood and skin tissue samples from psoriasis patients and to explore the underlying mechanisms both *in vivo* and *in vitro*.

Author contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and

agree to be accountable for all aspects of the work.

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Ethical approval

The study protocol was approved by the Ethics Committee of the Second Affiliated Hospital, Harbin Medical authorized the study protocol (GZR2023-06).

Conflict of interest

The authors have not identified any potential conflicts of interest.

Data availability statement

Data supporting the findings of this study are available from the corresponding author upon reasonable request.

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